B) Non-Technical Abstract

Melanoma is the seventh most common cancer in the United States, and is second to leukemia in terms of the "years of potential life lost" among all cancers because it appears at a relatively young age and the treatment of advanced melanoma has minimal impact on survival. The discovery of melanoma associated antigens (tumor markers that can be recognized by the immune system) has opened the door to new treatment strategies based on the stimulation of an effective immune response. MART-1/Melan-A is one of the best characterized antigens. Although an immune response to MART-1 can be demonstrated in the laboratory, the immune system does not get rid of MART-1-expressing melanomas in patients because the cancer cells are not specially equipped to present these melanoma antigens to the immune system. Dendritic cells are the most powerful immune stimulating cells known. They are naturally suited for antigen presentation because they have a higher amount of specialized proteins for antigen presentation (major histocompatibility complex molecules class I and II) than other cells, together with the expression of important "costimulatory molecules" that enhance the immune system's response to antigens. Recently, several investigators have reported that cells obtained from blood can be made into dendritic cells by culture in the laboratory in a combination of two cytokines, GM-CSF and IL-4. These cultured dendritic cells have been shown to be superior to other antigen presenting cells for the generation of specific tumor-killing cells (cytotoxic T cell lymphocytes).

Our hypothesis is that the introduction of the MART-1 melanoma antigen DNA into dendritic cells will stimulate an effective immune response capable of attacking MART-1-expressing cancer cells in advanced melanoma patients. In previous studies we have shown that dendritic cells can process and present MART-1 products and are able to activate T cells to attack melanoma cells, and that the most efficient way to insert foreign DNA into the dendritic cells is using genetically engineered defective virus (adenoviral vectors) that are not able to make copies of themselves. We have also shown in the mouse that dendritic cells obtained in a similar way and engineered to express the MART-1 gene are able to protect mice from MART-1-expressing cancer cells.

The protocol design is intended to establish the toxicity, immunological and antitumor effects of MART-1 melanoma antigen gene-modified dendritic cells. We will initially treat 3 patients at the lower dose of gene-modified dendritic cells administered intradermaly and closely monitor any adverse effects. Next, 3 patients will be treated at the same dose level but intravenously. Four other groups of 3 patients each will receive increasing doses of antimelanoma dendritic cell vaccines either intradermaly or intravenously when the safety of the previous dose and route of dendritic cell administration is clearly established. All patients will be closely monitored for any adverse effect, changes in the immunological response and the course of their melanoma.